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Human Genome Epidemiology (HuGE) Review

Variants in Estrogen Biosynthesis Genes, Sex Steroid Hormone Levels, and Endometrial Cancer: A HuGE Review

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Variants in genes involved in estrogen biosynthesis are likely to be important in the etiology of endometrial cancer. This review summarizes data on variants in seven genes in the estrogen biosynthesis pathway and their relation to circulating levels of sex steroid hormones in women and to risk of endometrial cancer. Little or no association was found between genotypes of the cytochrome P-450 genes *CYP11A1* (-528[*TTTTA*]n) or *CYP17A1* (*-34T*/*C*) or the 17β-hydroxysteroid dehydrogenase 1 gene *HSD17B1* (Ser312Gly) and levels of progesterone, androgens, or estrogens. The position *-34T*/*C* variant in *CYP17A1* appears to be associated with reduced risk of endometrial cancer, with those homozygous for the variant allele having about half the risk of those homozygous for the wild type. Linked variants in *CYP19A1* (intron 4 [*TTTA*]n, intron 4 [*TCT*] insertion/deletion, exon 10 *C*/*T*) are related to some hormone levels and, based on two studies, to risk of endometrial cancer. For other genes (*HSD3B1*, *HSD3B2, HSD17B2*), no information is available on these associations. Results indicate the need to study other variants and haplotypes in these genes, particularly *CYP17A1* and *CYP19A1*, as well as variants in other genes involved in hormone biosynthesis and metabolism pathways. Larger studies or combined studies that allow for investigation of gene-gene and gene-environment interactions are warranted.

androgens; *CYP11A1*; *CYP17A1*; *CYP19A1*; endometrial neoplasms; epidemiology; *HSD3B*; *HSD17B*

Abbreviations: *CYP11A1,* cytochrome P-450 11A1 gene; *CYP17A1,* cytochrome P-450 17A1 gene; *CYP19A1,* cytochrome P-450 19A1 gene; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; *HSD3B1,* 3β-hydroxysteroid dehydrogenase 1 gene; *HSD3B2,* 3β-hydroxysteroid dehydrogenase 2 gene; *HSD17B1,* 17β-hydroxysteroid dehydrogenase 1 gene; *HSD17B2,* 17β-hydroxysteroid dehydrogenase 2 gene; SNP, single nucleotide polymorphism.

Editor's note: *This paper is also available on the website of the Human Genome Epidemiology Network (http://www.cdc.gov/genomics/hugenet/).*

A unifying hypothesis for endometrial cancer etiology is the presence of excessive or prolonged exposure to estrogens unopposed by progesterone (1, 2). One approach to understanding hormonal carcinogenesis is to study variants in genes involved in hormone biosynthesis and metabolism in relation to both circulating hormone levels and risk of hormone-related cancers. This review includes variants of genes in the biosynthesis pathway. The underlying hypothesis is that variants that increase circulating levels of estrogens, and perhaps androgens, are likely to increase risk of endometrial cancer (3, 4), whereas those that increase progesterone are likely to reduce risk (5).

GENES AND GENE VARIANTS

Figure 1 presents a simplified outline of steps in estrogen biosynthesis. We investigated the genes illustrated because

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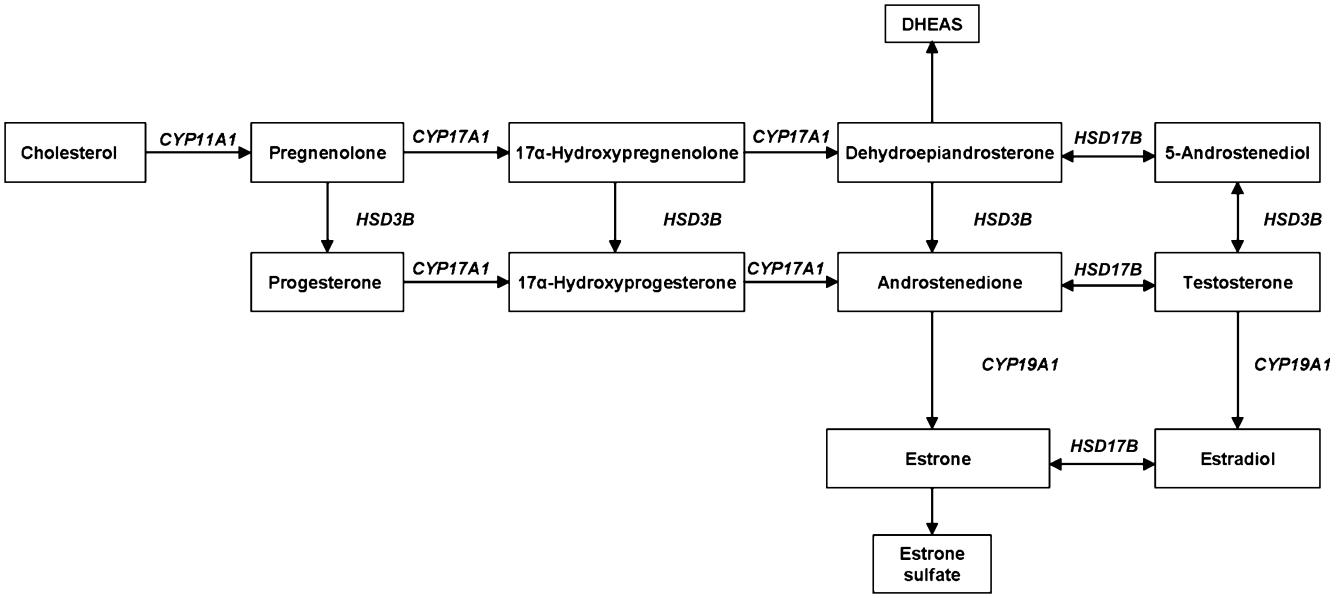

FIGURE 1. Steps in steroid hormone biosynthesis. DHEAS, dehydroepiandrosterone sulfate; *CYP11A1*, cytochrome P-450 11A1 gene; *CYP17A1*, cytochrome P-450 17A1 gene; *HSD17B*, 17β-hydroxysteroid dehydrogenase genes; *HSD3B*, 3β-hydroxysteroid dehydrogenase genes; *CYP19A1*, cytochrome P-450 19A1 gene.

they are directly in the estrogen biosynthesis pathway and are therefore likely to be related to hormone levels and risk of endometrial cancer, recognizing that many other genes involved in hormone biosynthesis, metabolism, and transport are also of potential interest. Web table 1 shows the location of each gene, its size, and the number and type of single nucleotide polymorphisms (SNPs). (This information is described in the first of eight supplementary tables; each is referred to as "Web table" in the text and is posted on the website of the Human Genome Epidemiology Network (http://www.cdc.gov/genomics/hugenet/reviews.htm) as well as on the *Journal*'s website (http://aje.oupjournals.org/).)

CYP11A1

Estrogens and other steroid hormones are derived from cholesterol, with pregnenolone formed from cholesterol through the activity of the cytochrome P-450 11A1 gene (*CYP11A1)*. Although 58 SNPs have been identified in *CYP11A1* (Web table 1), and some may be important to function based on sequence homology analysis (6), only one has been commonly studied in relation to hormone levels or disease: the pentanucleotide [*TTTTA*]n repeat (D15S520) at the -528 position in the promoter region. No functional differences have been reported for repeats of different lengths, which vary between four and 10.

CYP17A1

Other early steps in estrogen biosynthesis are the conversion of pregnenolone to 17α-hydroxypregnenolone and dehydroepiandrosterone (DHEA) and the conversion of progesterone to 17α-hydroxyprogesterone and androstenedione. The first steps, conversion of pregnenolone and progesterone, are carried out by 17α-hydroxylase and the second, conversion of 17α-hydroxypregnenolone and 17α-hydroxyprogesterone, by C17,20 lyase; both enzymes are products of cytochrome P-450 17A1 (*CYP17A1)* and are active in the ovary and adrenal cortex. Activity appears to be low in postmenopausal ovaries (7, 8) although elevated in the ovaries of postmenopausal women with endometrial cancer (8). The adrenal hormones, DHEA and its sulfated form dehydroepiandrosterone sulfate (DHEAS), are the primary pool of substrate for more active hormones, particularly in postmenopausal women.

As shown in Web table 1, 54 SNPs have been found in *CYP17A1*; however, only one has been commonly studied: a *T*/*C* change (often called *A1*/*A2*) at the *-34* position relative to the start codon in the 5′ promoter region. The *A2* allele of this SNP (*rs743572*) was originally thought to be associated with an Sp-1 binding site that would lead to higher expression (9), but a later study did not support this hypothesis (10), and the functional impact of the *T*/*C* change is not known. Haplotype structure has been described in two studies (11, 12) in which sequencing of multiple SNPs in *CYP17A1* was undertaken. Both of these studies identified three haplotypes that accounted for most of the variation in this gene.

HSD3B1 and *HSD3B2*

3β-hydroxysteroid dehydrogenases catalyze several reactions in the androgen pathway, leading to production of androstenedione and testosterone. They also catalyze the production of progesterone from pregnenolone. The two

genes, 3β-hydroxysteroid dehydrogenase 1 and 2 (*HSD3B1* and *HSD3B2)*, are located next to each other on chromosome 1p13 and share 93 percent homology, but they are active in different tissues. The HSD3B1 enzyme is expressed in the placenta, breast, and skin and in some tumors (13), whereas the HSD3B2 enzyme is expressed in adrenal glands, testis, and ovary. Uterine expression has been reported for both enzymes (14, 15). In addition to the SNPs in each of these genes (Web table 1), a complex dinucleotide repeat in intron 3 of *HSD3B2* has been reported (16, 17).

CYP19A1

Cytochrome P-450 19A1 (*CYP19A1)* codes for aromatase, the rate-limiting step in estrogen production. As indicated in Web table 1, 498 SNPs have been identified in this large gene. In addition to converting testosterone to estradiol in ovarian granulosa cells, aromatase converts androstenedione to estrone in adipose tissue. Expression appears to be highest in tissue from the buttocks, intermediate in tissue from the thighs, and lower in abdominal tissue (18). The gene has tissue-specific promoters (19) with different transcripts found in different tissues. Although not expressed in normal endometrium, *CYP19A1* is expressed in malignant endometrial tumors (20–23). The type II promoter, also found in gonadal tissue, and the type I.3, also found in adipose tissue, have been identified in endometrial cancer tissues (20).

Studies of this gene have focused on three variants that appear to be in linkage disequilibrium (24–27): a [*TTTA*]n repeat in intron 4, varying from seven to 13 repeats, with seven the most common; a nearby 3 base pair [*TCT*] deletion (*rs11575899*) found only in conjunction with the seven repeat (28, 29); and a *T*/*C* change in the 3′ untranslated region (exon 10, *rs10046*). The *TT* genotype appears to be linked to eight and longer repeats in the *TTTA* sequence (10, 24). Detailed studies of SNPs (30, 31) have shown a large number of haplotypes in this large gene.

HSD17B1 and *HSD17B2*

17β-hydroxysteroid dehydrogenase 1 and 17β-hydroxysteroid dehydrogenase 2 are responsible for reduction and oxidation of estrogens to more and less active forms, respectively. These enzymes function in an intracrine fashion, with actions produced in the same cells in which hormone metabolites are produced, without being reflected in the general circulation (32). The 17β-hydroxysteroid dehydrogenase 1 gene (*HSD17B1*) is responsible for the reduction (O → OH) of estrone to estradiol, the more bioactive estrogen; the 17β-hydroxysteroid dehydrogenase 2 gene (*HSD17B2*) is responsible for the oxidation of estradiol to estrone.

Studies of *HSD17B1* have focused on a nonsynonymous SNP (i.e., resulting in a change in amino acid) Ser312Gly (*A*/*G*) (*rs605059*). Sequence homology analysis indicates that this SNP is unlikely to affect function (6). Studies of haplotypes have identified three (33, 34) or four (35) common haplotypes that account for 97 percent or more of chromosomes in Caucasians. We found no association studies of polymorphisms or haplotypes in *HSD17B2*.

DISEASE: ENDOMETRIAL CANCER

More than 41,000 women in the United States will be diagnosed with uterine corpus cancer in 2006 (36), making this the most common gynecologic cancer; about 90 percent of these cancers are epithelial cancers (37). Data from the Surveillance, Epidemiology, and End Results (SEER) Program (http://www.seer.cancer.gov/statistics) indicate that it is largely a disease of postmenopausal women, with a median age at diagnosis of 63 years. The overall annual incidence rate in the United States, based on SEER data, is 29.2 per 100,000; age-specific incidence is highest among women aged 70–79 years, exceeding 100 per 100,000 per year. SEER data are based on all women, including those not at risk because they have had their uteri removed through hysterectomy; the incidence rate among women at risk is higher by 67 percent, or 48.7 per 100,000 (38).

Most established risk factors for endometrial cancer have in common prolonged or excessive exposure of the endometrium to unopposed estrogens. Estrogen-only therapy is a clear risk factor, evidenced by many studies (39–42). Other risk factors for endometrial cancer (43, 44) such as nulliparity, early menarche, and late menopause, as well as the protective effect of smoking (45) may also operate through an estrogen-related pathway.

Obesity has consistently been found to increase risk of endometrial cancer, with odds ratios for the highest category of weight or body mass index usually between 2 and 3 and most studies finding significant trends with increasing weight (46). In postmenopausal women, obesity is an important predictor of circulating estrone and estradiol levels (47–50), reflecting conversion of androgens in adipose tissue (51). In addition, obesity is associated with lower levels of serum hormone binding globulin (49), leaving more estradiol available to target tissues. In premenopausal women, levels of estrogen are high regardless of weight (49, 52), and risk of endometrial cancer in overweight women is attributable to reduced levels of progesterone (2).

Hormone levels have been measured directly in case-control and cohort studies of endometrial cancer. Compared with controls, postmenopausal endometrial cancer cases have been found to have higher circulating levels of estrone and androstenedione (4, 53), even after controlling for body mass index and other factors. Prospective studies in postmenopausal women (3) have shown strong associations between serum levels of estradiol and estrone and subsequent development of endometrial cancer, after adjustment for body mass index and other potential risk factors. Circulating levels of androgens were also positively related to risk, but the associations were small, and, after controlling for estrogens, only levels of DHEAS remained significantly elevated.

ASSOCIATIONS WITH HORMONE LEVELS AND ENDOMETRIAL CANCER

Studies were identified through searches in PubMed (http://www.nlm.nih.gov/entrez) covering the period 1966 through November 2005 for the name of the genes of interest—*CYP11A1*, *CYP17A1*, *HSD3B1*, *HSD3B2*, *CYP19A1*, *HSD17B1*, and *HSD17B2*—in combination with the term

TABLE 1. Results of studies of variants in estrogen biosynthesis genes and risk of endometrial cancer

Gene	First author	Year	Reference no.	Population	Study design	No. of cases	No. of controls	Polymorphism	Genotype	OR*	95% CI*
CYP17A1	Haiman†	2001	71	Not specified	Nested case-control	184	554	*-34 T→C (A1→A2)*	*A1/A1*	1 (Ref*)	
								rs743572	*A1/A2*	0.96	0.64, 1.44
									A2/A2	0.44	0.22, 0.87
	Berstein‡	2004	78	Not specified	Case-control	165	188	*-34 T→C (A1→A2)*	*A1/A1*	1 (Ref)	
								rs743572	*A1/A2*	1.28	0.80, 2.06§
									A2/A2	0.48	0.25, 0.91§
	Szyllo¶	2006	80	Polish	Case-control	100	106	*-34T→C*	*TT*	1 (Ref)	
								rs743572	*TC*	0.56	0.28, 1.13§
									CC	0.53	0.25, 1.11§
	Aban #	2006	79	Turkish	Case-control	57	35	*-34T→C (A1→A2)*	*A1/A1*	1 (Ref)	
								rs743572	*A1/A2*	0.26	0.09, 0.74§
									A2/A2	0.50	0.10, 2.60§
	McKean-Cowdin**	2001	81	African American, Japanese, Latina, non-Latina White	Nested case-control	51	391	*-34 T→C (A1→A2)* *rs743572*	*TC/CC* vs. *TT*	0.62	0.34, 1.12§
CYP19A1	Paynter††	2005	27	Not specified	Nested case-control	220	666	Intron 4 [*TTTA*]n	7/7	1 (Ref)	
									7/>7	1.97	1.25, 3.12
									>7/>7	1.92	1.17, 3.14
	Berstein‡	2004	78	Not specified	Case-control	136	116	Intron 4 [*TTTA*]n	7/7	1 (Ref)	
									7/>7	2.74	1.34, 5.60§
									>7/>7	3.26	1.53, 6.93§
	Paynter††	2005	27	Not specified	Nested case-control	220	666	Intron 4 [*TCT*] insertion/deletion	Ins*/Ins	1 (Ref)	
									Ins/Del*	0.80	0.56, 1.14
									Del/Del	0.71	0.39, 1.27
	Paynter††	2005	27	Not specified	Nested case-control	220	666	3′ UTR* (exon 10) *C→T*	*CC*	1 (Ref)	
								rs10046	*CT*	1.79	1.13, 2.86
									TT	1.82	1.11, 3.00
	Paynter††	2005	27	Not specified	Nested case-control	220	666	5′ flank (*G→A*)	*GG*	1 (Ref)	
								rs4775936	*GA*	1.72	1.11, 2.66
									AA	1.83	1.12, 2.99
	Paynter††	2005	27	Not specified	Nested case-control	220	666	Haplotype C	Haplotype C vs. all others	1.26	0.96, 1.66
	Szyllo¶	2006	80	Polish	Case-control	100	106	Exon 3 *G→A*	*GG*	1 (Ref)	
								rs700518	*GA*	0.82	0.41, 1.63§
									AA	0.68	0.33, 1.40§

HSD17B1	Setiawan‡‡	2004	33	Not specified	Nested case-control	222	666	*Ser312Gly (A→G)* *rs605059*	*GG*	1 (Ref)
									AG	1.09 0.71, 1.67
									AA	1.27 0.80, 2.02

* OR, odds ratio; CI, confidence interval; Ref, referent; Ins, insertion; Del, deletion; UTR, untranslated region.

† Inclusion criteria: no hysterectomy, no history of cancer except nonmelanoma skin cancer. Controls were matched to cases on year of birth, menopausal status at blood draw and diagnosis, hormone replacement therapy at blood draw and diagnosis (current vs. not current), time of day, month, and fasting status at blood draw. Adjusted for matching variables and body mass index, weight gain since age 18 years, age at menarche, parity, age at first birth, duration of postmenopausal hormone use, history of oral contraceptive use, pack-years of smoking, first-degree family history of endometrial and colon cancer. Includes incident and prevalent cases.

‡ Inclusion criteria: no oncologic or other serious chronic or acute disease in controls.

§ Calculated from data given in the paper.

¶ Inclusion criteria not specified. DNA from paraffin-embedded tissue for cases and normal endometrial tissue for controls.

Inclusion criteria: controls had endometrial biopsies in the previous 12 months with suspicion of endometrial pathology but resulting in normal endometrial histopathology.

** Inclusion criteria: age 60 years or older.

†† Inclusion criteria: no hysterectomy, no history of cancer except nonmelanoma skin cancer. Adjusted for year of birth, menopausal status, use of postmenopausal hormone therapy, time of day, month, fasting status at blood draw, body mass index, weight gain since age 18 years, lifetime pack-years of smoking, age at menarche, first-degree family history of endometrial or colon cancer, age at menopause, parity and age at first birth, age at last birth.

‡‡ Inclusion criteria: no hysterectomy, no history of cancer except nonmelanoma skin cancer. Adjusted for year of birth, menopausal status, use of postmenopausal hormone therapy, time of day, month, and fasting status at blood draw, body mass index at age 18 years, weight gain.

"polymorphism" or the term "haplotype" and for the combination of "endometrial cancer" and "polymorphism" or "haplotype." This process was supplemented by manual searches for other articles in those papers that included genotypes and hormone measures or that compared genotypes of endometrial cancer cases and controls. We included original peer-reviewed publications in English that reported on genotypes and steroid hormone levels in serum or plasma of normal women and studies that compared women with and without endometrial cancer with respect to genotype. We excluded studies that presented combined results for cases and controls (54–57), involved women with unusual characteristics (58), or were subsequently updated with larger samples (59–61). Several studies were small: of the 25 studies that compared hormone levels according to genotypes, seven had fewer than 100 respondents; of the seven studies of association of genotypes with endometrial cancer, two had fewer than 100 cases. We included data on the following hormones: progesterone, 17-hydroxyprogesterone, DHEA, DHEAS, androstenedione, testosterone, free testosterone, estradiol, free estradiol, estrone, and estrone sulfate. The ratios of estrone/androstenedione, estradiol/testosterone, and estradiol/free testosterone for *CYP19A1* and the ratio of estradiol/estrone for *HSD17B1* are also reported in this review. The studies varied in the specific hormones included.

For three of these genes, *HSD3B1*, *HSD3B2*, and *HSD17B2*, we found no studies of variants in association with either hormone levels or risk of endometrial cancer. Web tables 2−8 summarize studies of genotypes in each of the other genes and hormone levels, showing the first author and year, country, ethnicity, menopausal status, number of women, source of subjects, genotype, prevalence, levels of steroid hormone associated with each genotype (in units as given in each paper), and statistical significance of differences in hormone levels between genotypes. In each table, data are arranged by hormone, menopausal status, and date of publication. For studies of genotypes and risk of endometrial cancer, table 1 shows the first author and year, population, study design, numbers of cases and controls, the polymorphism studied, the genotypes compared, and the odds ratio and 95 percent confidence interval for the comparison of cases with controls. Inclusion criteria and variables adjusted for in analysis are given in footnotes to each table.

CYP11A1

Hormone levels. As shown in Web table 2, the five studies of associations of the pentanucleotide [*TTTTA*]n repeat (D15S520) at the -528 position in *CYP11A1* with hormone levels in normal premenopausal women have shown no associations with levels of progesterone, androgens, and estrogens by genotype (62–66). Similar results were found in the single study of postmenopausal women (67), although this study in China found marginally higher levels of estradiol in women without any eight repeat alleles.

Endometrial cancer. To our knowledge, no published papers have addressed associations of genotypes at the -528[*TTTTA*]n repeat, or other polymorphisms in *CYP11A1,* with endometrial cancer.

CYP17A1

Hormone levels. For *CYP17A1*, we identified 12 studies that reported on the association of hormone levels with the position *-34T/C* variant. Web table 3 shows results for progesterone or 17-hydroxyprogesterone, DHEA and androstenedione (the hormones most likely to be related to the activity of *CYP17A1* based on the pathway outlined in the figure), and DHEAS, testosterone, and free testosterone. One study found a trend toward higher levels of progesterone among premenopausal women with number of *A2* alleles (68), but this finding was not supported by other studies (65, 69, 70). Genotype does not appear to be associated with DHEA or androstenedione (65, 70–72). Similarly, studies of DHEAS, testosterone, and free testosterone, indirectly influenced by *CYP17A1*, have not shown an association with genotype in premenopausal or postmenopausal women (62, 65, 70–75). The exception was one study (69) that found the variant *A2* allele to be associated with higher DHEAS in premenopausal women, but not in postmenopausal women. These studies varied in the potential confounders they controlled for: about half controlled for age, whereas others controlled for body mass index and race or ethnicity, and for variables related to the blood draw. Overall, there is little or no evidence of an association between this variant in *CYP17A1* and androgen levels.

Some evidence has been found of an association of this *CYP17A1* polymorphism with estrogens (Web table 4). In postmenopausal women, an association between the *A2/A2* genotype and higher levels of estrone was reported initially by Haiman et al. (59), with significantly higher levels for women with the *A2/A2* genotype compared with the *A1/A1* genotype ($p < 0.01$; data not shown); however, an expansion of this study showed weaker results that were of borderline significance ($p = 0.05$) (71). Other studies of estrone (70, 72, 76) and estrone sulfate (71) showed no consistent association. For estradiol, an early study reported the number of *A2* alleles to be associated with higher levels of estradiol in premenopausal women (68); however, subsequent studies in premenopausal women did not replicate these results (65, 69, 75–77). In postmenopausal women, while one study (69) reported significantly higher levels of estradiol levels in women with the *A2/A2* genotype, others found no significant differences (70–72, 77). Most of these studies adjusted for age and body mass index; adjustment for other factors was less consistent.

Although haplotypes for this gene have been identified in studies of prostate cancer (11) and lymphoma (12), the association of haplotypes with hormone levels is not known to have been reported. In both studies that assessed haplotypes, three common haplotypes were reported, with the *-34 A2* (*C*) allele found on the two less common of these three haplotypes.

Endometrial cancer. Because of early findings that the *A2* allele was associated with a more active binding site (9) and with higher levels of estradiol (68) and estrone (59), this variant might have been expected to increase risk of endometrial cancer. However, five published studies have reported lower risk associated with this variant (table 1). Comparing the homozygous variant *A2/A2* with the homozygous wild-type *A1/A1*, four studies indicated that risk was about half (71, 78–80). In the fifth study, comparing any variant (any *A2*) with the homozygous wild type, an odds ratio of 0.62 (95 percent confidence interval: 0.34, 1.12) (81) was reported. (Odds ratios and confidence intervals for four of these studies (78–81) were calculated from data given.) Although results for the homozygous variant genotype were consistent across studies, results for heterozygotes were not. Two of these studies were case-control studies nested in cohorts, the Nurses' Health Study (71) and the Multiethnic Cohort (81). The other studies were hospital-based case-control studies (78–80). Only one of these studies (71) adjusted for potential confounders, including both design variables and risk factors potentially associated with endometrial cancer; however, adjustment made little difference in the odds ratio. Two studies were small, with only 57 (79) and 51 (81) cases. To our knowledge, association of other polymorphisms in *CYP17A1* with endometrial cancer, or of haplotypes, has not been reported.

CYP19A1

Hormone levels. We identified 13 studies that investigated the association of one or more variants in *CYP19A1* with circulating hormone levels. Because aromatase converts androstenedione to estrone and testosterone to estradiol (figure 1), different activity of the variants might be expected to affect levels of any of these hormones and the ratios between them. Studies of the relation of the [*TTTA*]n repeat (Web table 5) to progesterone or androgen levels showed no differences according to the number of repeats (65, 72, 82). For estrone, estrone sulfate, and estradiol, some differences were observed according to the number of repeats, but there was no consistent pattern across studies. Three studies found no differences (65, 77, 83); these studies differed regarding the menopausal status of the women included and the way in which genotypes were classified. Three studies of postmenopausal women reported differences in hormone levels, but the findings were inconsistent. Haiman et al. (82) found lower levels of estrone sulfate (but not estrone or estradiol) among women with at least one 7 repeat allele, but they found no differences for any of the estrogens according to the number of eight repeat alleles. Tworoger et al. (72) found higher levels of estrone, estradiol, and free estradiol among women with one or more eight repeat alleles. Comparing women with and without seven repeats alleles but without the associated 3 base-pair deletion, they did not find any differences. Dick et al. (84) found higher levels of free estradiol (but not total estradiol) among women with at least one seven repeat allele but without the associated 3 base-pair deletion. The ratio of estrone to androstenedione was found to be higher in women with at least one 8 repeat allele in one study (82), although a smaller study of African Americans did not find a difference (85). Overall, while some reported associations with estrogens have been reported, the results are conflicting and inconclusive.

As shown in Web table 6, there were five studies of the 3 base-pair *TCT* insertion/deletion polymorphism. One study included 17-hydroxyprogesterone, finding no differences (70). Three of these studies investigated androgens, with

some significant associations reported, but not consistently: one study found higher levels of androgens (DHEAS, androstenedione, free testosterone) among those with any deletion (86); another found higher androstenedione and testosterone among heterozygotes but not among homozygotes for the deletion (72); and a third found no differences (70). Two studies comparing levels of estrone and estradiol among women according to the presence of this polymorphism (70, 72) found significant trends, with the number of *TCT* insertions associated with higher hormone levels. Other studies (77, 86, 87) did not. Both of the studies that analyzed the ratios between estrogens and androgens (70, 86) found higher ratios in women homozygous for the insertion.

As shown in Web table 7, four studies investigated the *C*/*T* change in the 3′ untranslated region in postmenopausal women. No differences were noted in progesterone levels in one study (70). Haiman et al. (24) found trends toward lower levels of several androgens (DHEA, DHEAS, androstenedione) according to the number of *T* alleles but no differences for estrone or estradiol. In contrast, Dunning et al. (70) found trends toward higher levels of estrone and estradiol according to the number of *T* alleles but no differences for androgens; the other two studies found no association (27, 77). Three of the four studies (24, 27, 70) looked at the ratio of estradiol to testosterone and/or estrone to androstenedione, finding either the ratio highest for the *TT* genotype or a dose-response relation for the number of *T* alleles.

In addition to those polymorphisms in *CYP19A1* shown in Web tables 5–7, one study (88) investigated testosterone and estradiol levels in relation to four SNPs (previously shown to be useful for tagging haplotypes (30)) in a study of 109 British (mainly Caucasian) women aged 18–25 years recruited from general practice surgeries and advertisements. For one of these SNPs (*rs2414096*), a *G*/*A* change in intron 2, the less common *A* allele, was associated with higher levels of both of these hormones, but there was no difference for the ratio of estradiol to testosterone. For the other SNPs, there were no significant differences in hormone levels (data not shown).

Four studies have investigated linkage disequilibrium in *CYP19A1*, with similar results (27, 30, 31, 57). Using closely spaced markers, Haiman et al. (30) identified four blocks; the polymorphisms described above are categorized into one block. Paynter et al. (27) identified a common haplotype associated with a higher ratio of estrone to androstenedione and of estradiol to testosterone.

Endometrial cancer. Two studies have reported on the association of *CYP19A1* genotypes with risk of endometrial cancer (table 1). Berstein et al. (78), in a hospital-based case-control study in Russia, found increased risk associated with longer repeats (>7) in the intron 4 *TTTA* polymorphism; the odds ratio (calculated from the data given) for those having both alleles >7 repeats was 3.26 (95 percent confidence interval: 1.53, 6.93). Paynter et al. (27), in a case-control study nested in the Nurses' Health Study, also found increased risk for women with longer alleles: odds ratio for those having both alleles >7 repeats = 1.92 (95 percent confidence interval: 1.17, 3.14), adjusted for several potential confounders. Odds ratios of similar magnitude were found for those with the *TT* genotype in the 3′ untranslated region and for other SNPs in the same region; however, no significant difference was found for the 3-base-pair deletion. For each of these polymorphisms, similar results were found for the heterozygous and the homozygous variant genotypes. The adjusted odds ratio for the haplotype including these changes was 1.26 (95 percent confidence interval: 0.96, 1.66).

HSD17B1

Three studies examined a Ser312Gly (*A*/*G*) (*rs605059*) change in exon 6 of the *HSD17B1* gene (Web table 8) in relation to estrone and estradiol, all finding no association (33, 70, 77). One of these studies (33) also reported no association between two intronic SNPs (+1,004 *C*/*T* and +1,322 *C*/*A*) and estrone, estradiol, and estrone sulfate (data not shown). Studies of haplotypes have identified three (33, 34) or four (35) common haplotypes that account for 97 percent or more of chromosomes in Caucasians. The only known study to date of endometrial cancer, a nested case-control study in the Nurses' Health Study, found no association of genotypes or haplotypes with disease (33) (table 1).

DISCUSSION

Only four of the genes in the estrogen biosynthesis pathway that were included in this review (*CYP11A1*, *CYP17A1*, *CYP19A1*, and *HSD17B1*) have been studied with respect to their association with levels of steroid hormones in normal women, and three have been studied regarding risk of endometrial cancer. For *CYP11A1*, only one polymorphism has been investigated, with mainly null results. Nearly all published studies focused on premenopausal women. To our knowledge, no studies on the relation of *CYP11A1* polymorphisms and endometrial cancer risk have been published. *CYP11A1* is responsible for the first step in hormone biosynthesis, and, if variants are important, they may be so only in combination with those in other genes.

For *CYP17A1*, while earlier studies (59, 68) showed a possible association between the *C*/*C* (*A2*/*A2*) genotype and higher estrogen levels, and an earlier review concluded that genotype influenced estrogen levels in premenopausal women (89), the weight of evidence now is that there is little, if any association with progesterone, androgens, or estrogens. The earlier review included six studies; ours included 12. Most of those added were published more recently. In addition, we excluded two of the six studies in the earlier review because they measured hormones in urine or follicular fluid. It is not clear how the *CYP17A1* genotype would affect estrogen levels when there is little evidence of an effect on androgen levels. Although only five studies have been conducted on the association of these genotypes with endometrial cancer, all found reduced risk for the *C*/*C* (*A2*/*A2*) genotype at position *-34* in *CYP17A1*. These results need to be confirmed in larger studies; if confirmed, that would suggest another pathway through which this polymorphism affects risk. It has been noted that human *CYP17A1* converts very little 17α-hydroxyprogesterone to androstenedione (90, 91). Perhaps the protective effect of the *C* allele is

related to *CYP17A1*'s 17α-hydroxylase activity, which might affect levels of progesterone, although no association of genotype with progesterone levels was evident in the four studies reviewed. Other polymorphisms in the gene linked to this promoter site may have functions that affect risk.

For *CYP19A1*, some associations of genotypes with hormone levels have been found. The genotypes studied are in a large block showing linkage disequilibrium. Most consistent among these findings are results showing differences in the ratios of estrogens to androgens according to genotypes. Five of the seven studies examining ratios of estrone to androstenedione and/or estradiol to testosterone for various genotypes found differences for these linked polymorphisms (24, 27, 70, 82, 86), whereas two smaller studies did not (85, 88). For one of the variants studied, these results are consistent with a study of endometrial cancer risk: the *TT* genotype in the 3′ untranslated region was found to be associated with both higher estrogen ratios (24, 27, 70) and higher risk (27). For other variants, those associated with higher ratios were also associated with risk, although all results were not statistically significant: women with no seven repeat alleles had somewhat higher estrogen-to-androgen ratios (82) and were at higher risk of endometrial cancer (27, 78); women homozygous for the *TCT* insertion had higher ratios (70, 86) and a slightly higher risk of endometrial cancer (27).

For *HSD17B1*, there is no evidence, based on three studies (33, 70, 77), that genotypes in the exon 6 polymorphism (*rs605059*) are related to levels of circulating estrogens. Because this enzyme functions in an intracrine manner, its activity might not be expected to be reflected in the circulation. The one study of association of genotype and haplotypes with endometrial cancer did not indicate that variants in this gene influence risk (33). The null findings for the exon 6 polymorphism are consistent with a study using computational biology methodologies that indicated that this change is unlikely to be important in its effect on the protein (6).

This review is limited by the small amount of information available for several of these genes in terms of either hormone levels or association with endometrial cancer. Published reports for *CYP11A1*, *CYP17A1*, *CYP19A1*, and *HSD17B1* have focused on only a few polymorphisms, although, for each of these genes, and for *HSD3B1*, *HSD3B2*, and *HSD17B2*, there is a large number of other variants, as shown in Web table 1. The function of the polymorphisms included in this review, many of which are in noncoding regions, is unknown. With some exceptions (as noted above for *CYP17A1* and *CYP19A1*), little work has been published on the haplotype structure of these genes; data in the International HapMap Project (http://www.hapmap.org) are quite limited in terms of the number of polymorphisms investigated for each gene. These genes, and others, are part of a complex pathway of steroid hormone biosynthesis and metabolism, and it is likely that variants in the genes are important in conjunction with variants in other genes.

The small size of many studies resulted in insufficient power to identify differences among genotypes and in imprecise estimates of associations. Publication bias for small studies, particularly for associations with endometrial cancer, cannot be ruled out. Studies differed in their inclusion criteria and the variables controlled for in analysis; it was not possible to evaluate the effects of these criteria or adjustments on the results. Measurement error in assessing sex steroid hormone levels may have attenuated differences in hormone levels. Most studies were conducted among Caucasian populations, and prevalence of variants in these genes is likely to vary across racial and ethnic groups. Very few studies reported results stratified by variables other than menopausal status, so we were not able to evaluate possible stratum-specific results, although they have been reported in some studies (33, 58, 71).

There are also limitations related to our methods of conducting this review. We focused on results among ''normal'' women in studying the association of genotypes with hormone levels. In some instances, decisions about which studies to include were somewhat arbitrary; for example, we included one study in which participants were overweight and sedentary (72) and one in which most respondents were vegetarians or vegans (77), and we excluded one in which some women were from families with a genetic disease and some were related (58). Because the studies reviewed vary widely in the specific hormones studied, and only a few of the association studies included the same variants, we did not undertake a meta-analysis at this time.

LABORATORY TESTS

Genomic DNA extracted from blood was used for genotyping in all studies except two (65, 80), in which cells from cervicovaginal lavage or endometrial tissue were used. To identify SNPs and other polymorphisms, most studies used polymerase chain reaction, restriction enzymes, and gel electrophoresis, while some used other methods including direct sequencing, pyrosequencing, or TaqMan assays (Applied Biosystems, Foster City, California). Quality control measures varied and included use of duplicate blinded samples, controls of known genotype, and water blanks as negative controls. Some reports did not describe quality control measures in genotyping.

For hormone measures, most studies used radioimmunoassay, either direct (without extraction and purification) or indirect (with prior extraction and purification); other methods were also used. The studies that reported free testosterone and free estradiol used different methods of determining these values. Studies also varied in such factors as whether they used plasma or serum and whether they reported storage conditions. Quality control measures, including use of replicate samples and reporting inter- and intraassay coefficients of variation, were inconsistently reported.

POPULATION SCREENING

There is insufficient evidence to recommend screening at this time.

CONCLUSION AND RESEARCH PRIORITIES

A priority for future research is to investigate the associations of other variants in these genes and variants in the many other genes involved in steroid hormone biosynthesis

and metabolism with hormone levels and with endometrial cancer. As more is known about linkage disequilibrium and haplotype structure through the HapMap project and other studies, it will be important to determine the effects of variants likely to be inherited as a group. Because hormone biosynthesis genes are part of a complex pathway, it is likely that gene-gene interactions are important, as are gene-environment interactions with factors such as body mass index, body fat distribution, and use of estrogens. Larger studies or pooling of results among studies will be needed to obtain adequate power for these analyses. Overall, further study of variants in these genes and their impact on hormone levels and risk of endometrial cancer is likely to yield a better understanding of hormonal carcinogenesis.

INTERNET SITES

National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/ (dbSNP))

National Library of Medicine (http://www.nlm.nih.gov/entrez (PubMed))

National Cancer Institute (http://www.seer.cancer.gov/statistics (Surveillance, Epidemiology, and End Results))

International HapMap Project (http://www.hapmap.org (HapMap))

GeneCards (http://nciarray.nci.nih.gov/cards/(GeneCards))

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